A MONTHLY SCIENTIFIC PUBLICATION OF THE AMERICAN HEART ASSOCIATION, INC.

MODERN CONCEPTS OF CARDIOVASCULAR DISEASE

Copyright © 1961 by the AMERICAN HEART ASSOCIATION, INC., 44 EAST 23rd STREET, NEW YORK 10, N. Y.

Editor: E. COWLES ANDRUS, M.D. Associate Editor: RICHARD S. ROSS, M.D.
Editorial Office: JOHNS HOPKINS HOSPITAL, BALTIMORE 5, MARYLAND

RECEIVED
STATE UNIVERSITY
SEP 4 1962
UPSTATE MEDICAL CENTER
LIBRARY

Vol. XXX JULY 1961 No. 7

Susceptibility to Coronary Heart Disease *

■ **Thomas R. Dawber, M.D.**
Medical Director
Heart Disease Epidemiology Study
National Heart Institute
Lecturer in Gerontology
Harvard School of Public Health

William B. Kannel, M.D.
Associate Medical Director
Heart Disease Epidemiology Study
National Heart Institute
Clinical Associate in Preventive Medicine
Harvard Medical School

Increasingly reliable estimates of the prevalence and incidence of coronary heart disease are becoming available, which have tended to reinforce the concept of its importance as a contemporary health hazard in the United States, both in absolute terms and in relation to other diseases and causes of death. Cardiovascular disease is now the leading cause of death in the United States. Coronary heart disease (CHD) accounts for two-thirds of all heart disease. No important inroads into the morbidity or mortality of CHD have been made, in spite of earlier diagnosis and improvements in the therapeutic management. This is indicated by the fact that life expectancy in those aged 40 or over has increased only slightly in the past several decades.

Although it has been desirable to give increasing hope to the patient with CHD, it is important that all concerned recognize the seriousness of this disease. Examination of the natural history of CHD as it occurs in the whole community indicates that, once overt disease is recognizable, the odds are heavily weighted against the salvage of victims through therapeutic efforts alone.

The practicing physician, by training and experience, is concerned primarily with the recognition and treatment of disease. As his knowledge and experience increase, he is able to make diagnoses of disease at earlier stages when only minimal symptoms and signs are present. Health education at all levels seeks to make the patient aware of the importance of the earlier symptoms of an illness in order that he may seek medical advice as early as possible. Although the prevention of a disease is clearly the most desirable goal, if the disease is one for which treatment can be considered curative and from which the patient can be restored to his former state of health, the therapeutic approach may be all that is necessary and practicable. The need to develop preventive measures will appear most urgent in those diseases for which the mortality is high, treatment is unsatisfactory, or the patient who survives is liable to permanent disability even though an early diagnosis was made.

From observation of the manifestation of CHD, as it occurs in the community, it appears that this disease is one in which preventive measures will be required if an appreciable salvage of coronary victims is to be achieved.

Sudden Unexpected Death

Coronary heart disease becomes manifest as three major clinical entities: sudden unexpected death, myocardial infarction, and angina pectoris.

* From the Heart Disease Epidemiology Study, Framingham, Massachusetts, and the National Heart Institute, National Institutes of Health, U. S. Public Health Service, Department of Health, Education, and Welfare, Washington, D. C.

Although the occurrence of sudden unexpected death (death in a matter of minutes) may be due to several pathological entities, there is general agreement that most sudden deaths in the adult population are due to disease of the coronary arteries. Data from the Framingham Study indicate that sudden death accounts for approximately one-sixth of all CHD.[1] The proportion is even higher when men only are considered. This important "sudden death" group is seldom accounted for in studies of mortality in CHD, since rarely is it incorporated in most hospital statistics. A program of prevention, if available, is clearly the only aid which could be offered to these unfortunate individuals.

Myocardial Infarction

Myocardial infarction due to atherosclerotic coronary disease makes up the largest group of CHD. A review of individuals with a recognized myocardial infarction indicates that, although the majority survive to lead a useful life for many years, there is in fact a seriously high mortality within the first three weeks following the development of the infarction. From observations in the Framingham Study, of those surviving the initial infarction to enter a hospital, as many as 16 per cent of men and 32 per cent of women die shortly after admission, in spite of the best therapeutic efforts available. The immediate mortality from CHD (sudden death and death within the first three weeks) is therefore in the neighborhood of 40 per cent.[2]

Another sizable subgroup of myocardial infarction which is not ordinarily brought under medical supervision is the silent or unrecognized myocardial infarction. This group constitutes 20 per cent of all surviving patients with myocardial infarction.[3]

Angina Pectoris (and Coronary Insufficiency)

Angina pectoris indicates the presence of inadequate coronary blood flow, and represents the only type of coronary "heart disease" which can be diagnosed prior to pathological changes in the heart muscle. However, it does indicate an advanced state of coronary atherosclerosis. If it were possible to reverse the changes of atherosclerosis, these patients would constitute a salvageable group of CHD. Unfortunately, the presence of angina pectoris is often associated with already existing myocardial infarction.

It thus appears that a considerable proportion of patients with CHD found in the community can be helped only partially by therapeutic medicine. The answer clearly lies in attempts to prevent the disease before overt manifestations occur. Since it has been well established that coronary atherosclerosis is present many years prior to the development of symptoms of CHD, it is clear that prevention must begin many years before the appearance of clinically recognizable disease.

RECOGNITION OF THE CORONARY-PRONE INDIVIDUAL

A knowledge of the epidemiology of a disease is fundamental to the development of a program of disease prevention. From the study of the characteristics of persons who later develop CHD and comparison with the characteristics of those who remain free of this disease, it is possible many years before any overt symptoms or signs become manifest, and at a time in life when a preventive program might be instituted with some reasonable hope of success, to put together a profile of those persons in whom there is a high risk of developing CHD.

Certain of these risk characteristics have been clearly demonstrated. Others are still speculative and under investigation. As time goes on, more detailed information will become available which will allow a more precise indentification of highly susceptible individuals. It is hoped that physicians can prevent the development of overt CHD in susceptible individuals by altering these risk characteristics favorably. Many years will be required to establish proof of the efficacy of such efforts, but an attempt seems sound and reasonable, particularly since the measures required are perfectly consistent with acceptable health practices as we understand them today.

Several epidemiological studies have been in operation observing populations for factors capable of predicting the development of CHD. These ongoing, prospective, studies have involved the difficult task of closely observing population groups to determine the incidence of CHD and any factors which may be related to its development. A general population of a New England community has been observed at Framingham, Massachusetts, for the past 10 years.[4, 5] A group of civil servants in Albany, New York, has similarly been studied for a period of six years.[6] A study of civil service employees in Los Angeles has been carried on for over 10 years.[7] A group of business and professional men in the Minneapolis area has been followed for 13 years.[8] These studies rep-

resent the longitudinal observation of nearly 10,000 persons for a total of over 88,000 man-years' experience. In addition, many other investigators have been engaged in the study of special aspects of the epidemiology of CHD by the observation of selected groups. During this period of observation, a significant amount of new CHD has developed in these populations, permitting analysis of certain factors considered to be possibly related to the development of CHD. From these analyses, certain conclusions can be drawn.

SERUM CHOLESTEROL

Despite some confusion as to the importance of serum cholesterol, the significance of this risk factor in the development of CHD has been well established. Although the pathogenesis of the atherosclerotic lesion is not clearly understood, it has been recognized for many years that the principal constituent of the atherosclerotic plaque is cholesterol. Such knowledge has led to conjecture as to the mechanism for the deposition of cholesterol in these lesions. Many factors have been shown to influence the level of cholesterol in the serum: emotional stress, dietary constituents, physical activity, and various hormones, among others. Unfortunately, uncertainty concerning the mechanism responsible for the elevation of the serum cholesterol level has sometimes obscured its importance as a predictor of the development of CHD. However, in the studies mentioned above, in addition to the well-recognized importance of age and sex, the level of serum cholesterol stands out as the most significant.

Framingham data indicate that the average serum cholesterol level in adult males of a New England population is about 220 mg. per cent, with less than 5 per cent of the population having cholesterol levels below 160 mg. per cent and slightly more than 5 per cent having serum cholesterol levels over 280 mg. per cent. The serum cholesterol level in adult males does not appear to be an age-related characteristic; very little rise in average cholesterol level is observed in men between age 30 and 60. In adult women, on the other hand, the serum cholesterol level appears to be distinctly age-related, rising from an average of approximately 195 mg. per cent, for those aged 30, to a peak of 250 mg. per cent, at age 60.[2]

There is convincing evidence that serum cholesterol levels are definitely related, both to the presence of, and the development of, CHD. Animal experiments have shown a relationship between the production of elevated serum cholesterol levels and the development of atherosclerosis. Clinical studies have shown that the average serum cholesterol levels of persons who have developed CHD are definitely higher than in controls free of CHD. This demonstrates that there is a definite association between the elevated serum cholesterol level and existing CHD. It remained for the prospective studies of populations to demonstrate a relationship between pre-existing elevation of serum cholesterol and the subsequent development of CHD. From these studies, it is perfectly clear that when populations are divided into groups, according to levels of serum cholesterol, the incidence of newly developing CHD is observed to increase with each increment of cholesterol level. An example of the relative increase of risk in CHD associated with this characteristic is provided by the Framingham data (fig. 1). At the end of eight years

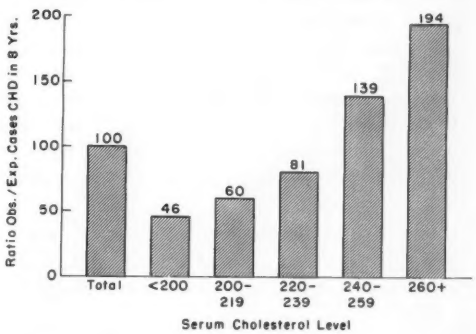

Figure 1. *Risk of developing CHD, according to cholesterol level in men, aged 30-59. Age and cholesterol level at time of entry into study.*

of observation in men with serum cholesterol levels below 200 mg. per cent, the rate was less than half that of the total population, while in the group with cholesterol levels of 260 mg. per cent, and higher, the rate was almost twice that of the total population, a total increase of fourfold. Similar results have been demonstrated in the other studies in Albany, Los Angeles, and Minnesota.

It is important to recognize that in the United States population, there is no level of serum cholesterol which can be called "normal" in the sense that such a level implies absence of risk of CHD. There is no level at which the risk takes a sudden rise. However, all other factors being equal, the lower the serum cholesterol, the lower the risk. Whether

some critical serum cholesterol level exists below which no relationship to CHD exists needs to be demonstrated in populations with naturally occurring low serum cholesterol levels. Since in the Framingham population there are few persons with serum cholesterol levels below 150 mg. per cent, it is not possible to determine the relative risk of persons with the "lowest levels" as observed in the U. S. A., i.e., persons who would be much nearer the average in other populations believed to have low CHD rates. It is likely that if it were possible to compare persons with cholesterol levels low by all population standards, e.g., less than 130, with those who have significantly higher levels, e.g., above 300, the risk would be far in excess of the fourfold increase demonstrated by a rise from 200 to 260, and over. It should therefore be clear that it is not appropriate to think of serum cholesterol levels as "normal" or "abnormal," since there is a steady rise of CHD incidence with increasing levels of serum cholesterol from low to high.

Consideration of whether action should be taken with regard to a given cholesterol level must be based on an appraisal of all other possible risk factors in addition to serum cholesterol per se. The risk associated with elevation of the serum cholesterol level appears to be greater for men than for women. Thus the increased risk associated with a rise in serum cholesterol from below 200 to 260, or over, in women is very slight, although further observation is needed to clarify this more exactly.

The relative risk associated with progressive elevation of the serum cholesterol level appears to decrease with advancing age. The significance of elevated cholesterol levels in younger persons is thus enhanced. Age and sex are therefore important factors to be considered in determining what action, if any, is indicated in persons with a given cholesterol level. Blood pressure level, as indicated below, is also of great importance in making this decision.

It must be recognized that if the cholesterol level is lowered by diet or drug therapy, it does not necessarily follow that the decreased risk of developing CHD accruing to persons with naturally occurring low cholesterol levels is automatically acquired. Much further study will be needed to evaluate the efficacy of such measures. Meanwhile, it seems reasonable to advocate measures which produce lowered serum cholesterol levels, especially in individuals considered highly susceptible to CHD on the basis of an evaluation of all the risk factors.

BLOOD PRESSURE LEVEL

Animal, experimental, and clinical evidence has clearly demonstrated that the atherosclerotic process is definitely accelerated and aggravated by an elevated blood pressure level. Although efforts to lower blood pressure levels have been undertaken primarily to alleviate or prevent development of heart enlargement, congestive heart failure, and other manifestations of hypertensive cardiovascular disease, it would appear that a no less deleterious effect of an elevated blood pressure level is the aggravation of the atherosclerotic process and the resultant early development of CHD.

Results of epidemiological studies have not been as consistent with regard to the significance of elevated blood pressure levels as they were with hypercholesterolemia. Nevertheless, when significantly large numbers of persons have been observed, there is general agreement that the higher the blood pressure level, the greater the risk of developing CHD in subsequent years.

In the Framingham Study, the average blood pressure level varied from approximately 135/80 for men at age 30, to 150/87 for men at age 60. The rise for women was somewhat greater, from 120/75 to 155/90. From the distribution curve of blood pressure levels, it does not appear that there are two distinct populations, one with hypertensive disease and the other normotensive, but rather that blood pressure is distributed "normally" with some excess in the upper levels.[9]

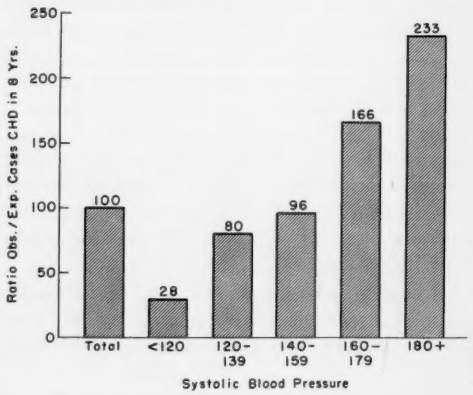

Figure 2. *Risk of developing CHD, according to systolic blood pressure in men and women, aged 30-59. Age at entry into study.*

Data from the Framingham Study, based on eight years of observation, show a striking effect of blood pressure level in the prediction of CHD (fig. 2). Those persons with systolic blood pressure levels below 120 mm. of mercury at initial examination, developed one-fourth of the amount of CHD which would have been expected for the age-sex composition of this group. However, the group with systolic blood pressure of 180, or over, developed over twice the amount of CHD expected. Thus, there was a ninefold increase in the risk of CHD with this gradient of blood pressure. Within these limits there was a smooth increment of increase with each increment of blood pressure studied. No critical level of blood pressure could be determined above which a sharp increase in risk occurred. Essentially the same gradient of risk was associated with each increment of diastolic blood pressure. Actually, there was a high correlation between systolic and diastolic blood pressure, with few persons having isolated elevations of either systolic or diastolic blood pressure. For this reason, it was not possible to assess the relative importance of systolic versus diastolic blood pressure.

As indicated above in the discussion of the significance of cholesterol level, the blood pressure level rather than the diagnostic blood pressure category is the important consideration, i.e., there is a gradient of risk within each diagnostic category, whether "normal" or "abnormal." However, the practicing physician, for reasons of practicability, is accustomed to classifying patients as hypertensive, normal, and possibly a borderline group requiring further observation. When the Framingham population was so classified, using both systolic and diastolic blood pressure, a gradient of risk was again demonstrated from normotensive to borderline to hypertensive levels.* Persons classified as "normotensive" had approximately one-half the expected risk, while "hypertensives" had a risk of one-and-a-half that to be expected. There was thus a threefold increase in risk of CHD in "hypertensives" as compared to "normotensives."

When in addition to elevated blood pressure, electrocardiographic findings of left ventricular hypertrophy (LVH) or x-ray evidence of cardiac enlargement are present, the risk of developing CHD is further augmented. Since persons with heart enlargement have, on the average, higher blood pressures than those with normal-sized hearts, it is necessary to examine the effect of this characteristic at various blood pressure levels. When this is done for LVH, it is apparent that at each blood pressure increment, the presence of LVH in the ECG further increases the risk of coronary heart disease by two to three times.

OVERWEIGHT

Data from life insurance companies have for many years indicated increased death rates from cardiovascular disease associated with obesity. Data from epidemiological studies tend to corroborate this finding (fig. 3). In

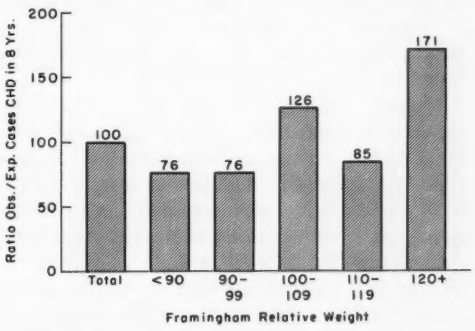

Figure 3. *Risk of developing CHD, according to Framingham relative weight in men, aged 30-59.*

the most obese, there is a slightly higher rate in both morbidity and mortality of CHD. There is a slight positive correlation between body weight, blood pressure, and serum cholesterol level. When these factors are taken into consideration, the independent contribution of excess weight to the risk of development of CHD becomes small indeed. However, because of the association between the easily identified characteristic of weight and the important factors of blood pressure and serum cholesterol level, reduction in weight is advisable because of a possible favorable effect on the other factors.

OTHER FACTORS

Many other factors, including emotional stress, physical activity, and smoking habits, among others, are under investigation in the various epidemiological studies. The evidence

* *Normotensive:* Below 140/90 on two independent observations. *Hypertensive:* Both systolic blood pressure determinations of 160 mm. of mercury, or over, and/or all diastolic blood pressures of 95, or over. *Borderline:* All others.

suggests that there is an increased risk of CHD in excessive cigarette smokers, in men who demonstrate low vital capacity, and in persons with higher levels of blood hemoglobin. However, further study is needed, not only in these factors, but in many others as well, before their association with the development of CHD can be clearly stated.

COMBINATIONS OF FACTORS

The risk associated with each of several easily determinable characteristics has been discussed. As these risk characteristics are combined in an individual, the susceptibility to CHD is greatly augmented and a more clear "coronary profile" emerges. As has been indicated, the risk associated with a blood pressure level of over 180 systolic is as much as ninefold, as compared to a level below 120 systolic, or from a diagnostic standpoint, the diagnosis of hypertension was associated with a threefold increase in the risk over a diagnosis of normotension. When the finding of left ventricular hypertrophy by electrocardiogram is added to hypertension, a further two- to threefold increase in risk occurs. If these two characteristics are found in the presence of a moderately elevated serum cholesterol, the risk is further compounded (fig. 4). Hence, a characteristic becomes more or less ominous, depending upon the age and sex of the individual and association with other risk characteristics. If we confine our attention to the three major risk characteristics thus far demonstrated—blood pressure, cholesterol level, and the electrocardiographic pattern of left ventricular hyperterophy—we can estimate the risk associated with combinations of these as follows: men 40-59, without electrocardiographic evidence of LVH and classified as normotensive, and with serum cholesterol levels in its lowest quartile, had only one-eighth the standard risk for this age group. Men in this age group without LVH, with blood pressure readings not classified as hypertensive, and with serum cholesterol levels under 250 mg. per cent, had approximately one-half the standard risk. Those with either hypertension, cholesterol level above 250 mg. per cent, and electrocardiographic evidence of LVH, had almost one-and-one-half times the standard risk. When two of these abnormal characteristics were present, the risk further increased, and when all these were present, the risk went up to four times that of the standard for the population. This latter group obviously constitutes a highly susceptible segment of the population.

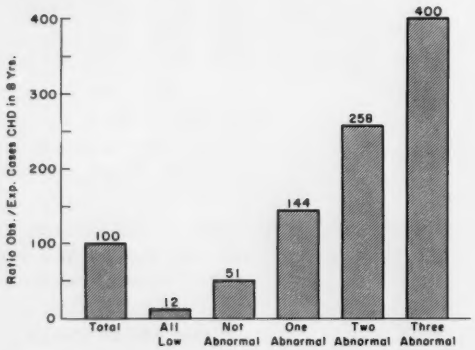

Figure 4. *Risk of developing CHD, according to combinations of blood pressure, serum cholesterol and ECG evidence of LVH in men, aged 40-59.*

It has seldom been possible in noninfectious diseases to identify such highly susceptible individuals years before the development of disease. The physician should be aware of his ability to do so, and should recognize the challenge it imposes in this serious contemporary health hazard which demands a primarily preventive rather than therapeutic approach.

REFERENCES

1. **Kannel, W. B., Dawber, T. R., Kagan, A., and Revotskie, N.:** Risk factors in the development of coronary heart disease; six years' follow-up experience: Framingham study. To be published.
2. **Dawber, T. R., et al.:** Framingham study. To be published.
3. **Stokes, J., III, and Dawber, T. R.:** The "silent coronary"; frequency and clinical characteristics of unrecognized myocardial infarction in the Framingham study. Ann. Int. Med. **50:** 1359, 1959.
4. **Dawber, T. R., and Kannel, W. B.:** Epidemiologic study of heart disease: Framingham study. Nutrit. Rev. **16:** 1, 1958.
5. **Dawber, T. R., Kannel, W. B., Revotskie, N., Stokes, J., III, Kagan, A., and Gordon, T.:** Some factors associated with the development of coronary heart disease; six years' follow-up experience in the Framingham study. Am. J. Pub. Health **49:** 1349, 1959.
6. **Doyle, J. T., Heslin, A. S., Hilleboe, H. E., Formel, P. F., and Korns, R. F.:** Measuring the risk of coronary heart disease in adult population groups: III. Prospective study of degenerative cardiovascular disease in Albany; report of three years' experience. 1. Ischemic heart disease. Am. J. Pub. Health **47** (suppl., April 1957): 25, 1957.
7. **Chapman, J. M., Goerke, L. S., Dixon, W., Loveland, D. B., and Phillips, E.:** Measuring the risk of coronary heart disease in adult population groups: IV. Clinical status of a population group in Los Angeles under observation for two to three years. Am. J. Pub. Health **47** (suppl., April 1957): 33, 1957.
8. **Keys, A., Taylor, H. L., Blackburn, H. B., Anderson, J. T., Simonson, E., and Brozek, J.:** Risk of coronary heart disease: Thirteen years of follow-up of 286 Minnesota men. To be published.
9. **Kagan, A., Gordon, T., Kannel, W. B., and Dawber, T. R.:** Blood pressure and its relation to coronary heart disease in the Framingham study. *In* Hypertension: Proceedings of the Council for High Blood Pressure Research, November 1958, vol. VII. New York, American Heart Association, 1959, p. 53.